PSJ3

Exhibit 82B

cell patients seem to have to sign contracts but cancer patients at elite institutions don't.

So I have a great concern about the discrimination that goes on about contracts that needs to be sorted out. So, that's one example.

I think that we are not saying everyone should have a contract but only some people should have a contract. And I have a concern that that could be misused for patients.

Q. When you say some people -- and I appreciate your concern for the poorer people and discrimination. Where you say some people have to have it, I am trying to understand how that fits in the context of your concern?

A. That we are identifying some groups at greater risk or at greater chances of misusing drugs. And we already know in this country that minorities are discriminated, they are inadequately treated for their pain. We know that they have less access to prescriptions, filling their prescriptions in New York pharmacies. That's been published.

We have evidence that their pain is untreated in a variety of settings. And I have a concern that these contracts might be used to

limit access to these treatments for certain populations of patients. So, I have a concern about that.

Q. I see. But this contract that Tennant & Olman are proposing I don't think is limited to a white or black issue, poor or rich.

A. No, I am broadly responding to the construct of do I agree with contracts or not contracts. So you are asking me do I agree with what they did, I am describing what they did. And I describe things that people say they say simply to be fair, to have that in the literature as a discussion. And that was the purpose of placing it here.

Q. I understand but I am trying to understand the answer you just gave in the context of how this would discriminate somehow. Are you saying that the people that would typically sign the contracts would fit into the category of the poorer class or --

A. That institutions would demand that certain people sign contracts and others would not.

Q. So, they wouldn't use them the way they are supposed to be used?

A. They might disuse -- there may be significant discriminatory practice associated with the use of contracts which might limit access to patients being adequately treated for their pain.

Q. The next sentence talks about, it says, they suggest -- is that referring to Tennant & Olman?

A. That is correct.

Q. The consent discussion includes risk of using alcohol, other drugs while taking opioids, the likelihood that a newborn will be physically dependent on opioids if these drugs are taken by a female patient during pregnancy and the possibility which the current data cannot refute absolutely that the psychological dependence to opioids can occur and may last a lifetime. Is that still true today?

A. Yes.

Q. Now, when you talk about psychological dependence, you are talking about addiction; is that correct?

A. I am quoting that but I am talking about addiction.

Q. You understand that the psychological

dependence to your way of thinking means addiction; is that right?

A. That is correct.

Q. And, do you agree with the statement that if somebody has psychological dependence or addiction that it may last a lifetime?

A. It's not my opinion. That's been an opinion that has been put forth by a variety of experts in addiction.

Q. And, you agree with that?

A. They are the experts and that's what they say.

Q. Well, you feel you are not qualified to comment on that?

A. No, I mean, I agree with it.

Q. You agree that addiction lasts a lifetime?

A. Yes.

Q. Addiction is something -- if you have addiction, if a patient has addiction, is it something that you have to treat?

A. No.

Q. Is it something that you have to tell the patient something about the condition so they can monitor it or --

A. I guess I think -- may I ask a question? I don't think I understand your question.

Q. You can ask that question. That's actually more of a statement than a question but --

A. Sorry about that. Could you repeat the question?

Q. Sure. If a person has addiction to opioids, do you agree that that condition lasts throughout the rest of their life?

A. Do you mean if a patient actually is addicted to opioids at that time?

Q. Yes.

A. Or has a history of addiction?

Q. Either one.

A. If the patient is actually addicted at a point in time, then that patient needs treatment. That patient needs to be tapered off their drugs and may need a treatment program.

Q. And, the treatment program can include what?

A. There are a variety of treatment programs. There are abstinence programs and there are drug free communities. There are

methadone maintenance programs. There is buprenorphine treatment. There are a variety of treatments for someone who has -- is actively abusing opioids and needs to be treated for that.

Q. And, again, you have used the word abusing?

A. Is actively abusing and is considered on a DSM four diagnosis to be substance dependent and addicted and meets all the criteria of that.

Q. Do you utilize the DSM four criteria when you would consider somebody to be addicted?

A. There are a variety of criteria that one might use but that's one of them.

Q. Is that in your opinion an acceptable criteria, DSM four?

A. In identifying addicts, yes. But it's a very complicated one to use in patients who have taken opioids in the setting of chronic pain.

Q. In terms of assessing a patient who has, potentially, addiction as defined by DSM four, would you agree -- you just used the word complicated, that that can involve a pretty thorough evaluation of the patient in order to make that diagnosis?

A. It involves a detailed history taking

from the patient.

Q. And, would you think that -- have you ever done that yourself?

A. Um-uh.

Q. Have you ever diagnosed someone with addiction to opioid medication?

A. Yeah.

Q. And, have you used the DSM four criteria to make that diagnosis?

A. Yeah, um-uh.

Q. And, you feel you are qualified to do that; correct?

A. That's right, um-uh.

Q. And, would you agree that psychologists and psychiatrists might be someone who would be qualified to make that type of determination?

A. Yes, um-uh.

Q. Now, on the next paragraph here, this is like towards the middle of the page, maybe going towards the bottom, it says here in a sentence -- and I will let you find it before I ask a question about it. If dose escalation continues to rise over several weeks or if a rapid rise in the absence of a documented change in disease occurs, it is recommended that the patient be

hospitalized in order to facilitate evaluation of the medical requirement -- medication requirement and if possible return to base line dose?

A. Um-uh.

Q. And, was that something that you agreed with in 1985?

A. I did. I agree with that.

Q. Is that still true today?

A. It would not be possible to admit the patient to a hospital any longer. The way that health care financing has changed, you would not be able to admit the patient to the hospital. That would not be possible.

Q. Well, would you agree that in lieu of admitting the patient to the hospital, the patient should be reevaluated?

A. Yes, and what the sentence is really suggesting is the reevaluation.

Q. And, possible return to base line dose?

A. Correct.

Q. Is the import of this that you just don't escalate the dosage of the drug without having a good reason to do it?

A. That is correct.

Q. And, that's still true today; right?

A. That is correct.

Q. It says, the next sentence, most patients in the surveys of opioid maintenance therapy published thus far have required modest doses of drugs. The need for relatively high doses must be especially scrutinized to insure that the drug is appropriately used and specifically the pain is the symptom being treated. Is that still true today?

A. Yes, it is.

Q. And, when you say that the pain is a symptom being treated, are you referring back to the possibility that there might be other factors involved in the patient's perception of pain?

A. Again, I would not say in the perception of pain but in their pain behaviors.

Q. Okay; I apologize but I am having trouble understanding that. If a patient comes into the office and says -- doctor says, do you hurt? And the patient says yes. And the doctor says, do you hurt on a scale of one to ten, one or ten, and the patient says ten. Is it -- in this sentence, are you saying that there is a concern that maybe when the patient says ten, there might be other things besides a

physiological reason for the pain that the patient says ten instead of three?

A. Yes, I agree with that.

Q. And, those factors might be social, economic, the things we talked about before; is that true?

A. They may be psychological, they may be social.

Q. Or economic; true?

A. Again, the economic, they could be economic but I continue to argue that economic indirectly impacts on psychological and social. And so I don't have -- I don't want to make a direct line of economic to --

Q. It's an indirect relationship, that is, the person -- if the person is in bankruptcy and they might be -- I am sorry, did you finish your answer?

A. Go ahead.

MR. HOFFMANN: I was trying to stop her from answering before you finished your question. That's why I put up my hand.

MR. COLANTONIO: So, you were trying to tell her not to continue the answer, that's a change.

MR. HOFFMANN: No, I was trying to tell her to let you finish your question.

MR. COLANTONIO: All right; thanks.

THE WITNESS: Sorry.

BY MR. COLANTONIO:

Q. So, the inferential relationship is if a person has bankruptcy or they have bad financial condition, they might be depressed. It might effect their psyche and therefore they might say I hurt ten instead of three as a factor; is that fair?

A. I agree with what you just said.

Q. The next sentence says, evidence of inappropriate use such as opioid intake to treat the depression or anxiety of such abuse behaviors as diversion or hoarding should be pursued and managed firmly. If control cannot be maintained, opiate therapy should be discontinued. That's true today; correct?

A. Yes, although, again, there is an evolving science now to recognize that opioid therapy may not be able to be discontinued because the patient is in severe pain and one has to provide them with better pain relief. So then the ethical responsibility of the physician to

take care of a patient, let's say, with, you know, advanced AIDS and severe chronic pain in the setting of drug abuse and so I think we have a more sophisticated and more organized approach to caring for patients that may end up in that situation.

Q. These guidelines we have been talking about, these concepts we have been talking about, you agree they apply not just to chronic pain but also to treatment of acute pain as well; right?

A. Well, I don't think I would want to say -- there is sort of a general conceptualization that you evaluate the patient, that you pay attention to all these issues, that pain can have many factors. But I think the distinction is patients with acute pain usually have an immediate cause for their pain, usually have a -- respond typically to the agents that are available and will taper off their drug. So they are different.

Q. So, they are different?

A. They are quite different. They are not taking the drug for this long period of time.

Q. They are different but the principles we have just gone through would still apply. For

example, you need to watch dose escalation, there should be a reason for it. You need to have fully informed consent and other things we have talked about would also apply to opioid treatment in an acute pain situation; right?

A. Well, I am not -- if patients are going to take an analgesic for an acute pain, a post operative pain, I am not sure that as general practice we fully inform them of every aspect of treatment since they are going to be on it for three days or five days and discontinue their drug. So I guess I am making a little bit of a distinction in the management.

And acute post-operative pain would be the best and most common model in this country. The patients are fully informed that they are going to receive a drug, it may be an opiate, those are the side effects. Those are pieces of information that they are provided with.

Q. Are you saying the informed consent given for patients on opioids more than three months should be different than that for acute situations?

A. Well, that's why we are talking about these guidelines for chronic pain.

Q. Well --
A. But, the general framework and principles are very similar.
Q. I think that was my point.
A. Okay.
Q. That the general framework and principles are similar. There may be some slight nuances that might apply to a chronic situation versus acute, but you still want to give the acute treatment informed consent; right? Or am I wrong?
A. Well, if by informed consent is that you want the patient to be knowledgeable about the treatment that they are receiving, then yes.
Q. Isn't that the purpose of informed consent?
A. Yes.
Q. And, in acute situations, you want to make sure you are treating a condition that can be described by physiological reasons, not social or economic or psychological reasons, correct?
A. That would be correct.
Q. I mean, those all apply across the board, whether acute or chronic?
A. Yes, but the risk of a patient taking a

drug for three to five days is different potentially than it is for taking it for 20 months or so.

Q. How so?

A. Because of the fact that the patient's pain will be diminishing rather than increasing and their dose requirements will be diminishing. So it is a different pattern of how they would take it.

Q. How about in terms of the potential for abuse and addiction, the risks of those?

A. Again, it is related to the duration of taking the drug. It is related to the dose. It's related to the setting and then of all the other factors that we talked about.

Q. So, you agree that addiction -- there is a relationship between dose and the risk of addiction?

A. Yes.

Q. You agree that there is a relationship between a person's social economic factors and potential for addiction?

A. That's described in the literature.

Q. You agree with that?

A. Sure.

Q. And, you agree that there is a relationship between the length of time on opiate medication and the potential for addiction?

A. Yes.

Q. Would you agree then that the rates of expected addiction for people in groups would be different based upon their social, economic, psychological factors, the dosing and the length of time that they are taking the drug?

A. I think that the development of addiction is individual. So I don't want to limit it to groups. It's an individual aspect. It depends on who the patient is.

Q. I suppose we could say that about -- I am sorry.

MR. HOFFMANN: Go ahead and finish your answer.

MR. COLANTONIO: That was mine.

THE WITNESS: It depends on who the patient is. This is probably the most important factor. And so -- and I would argue it depends much more on who the patient is than the drug.

BY MR. COLANTONIO:

Q. But, who the patient is includes social

setting, economic setting, psychological setting, those kinds of things; true?

A. Yes. Yes, it does.

Q. And, those all play a role --

A. Yes.

Q. I am sorry, you have to let me finish my question. Those all play a role to your way of thinking in the expected rate of addiction?

A. Yes.

Q. And, when you say it's individual in terms of expected rate of addiction to opioid medication, I mean, that's true for pretty much every disease and medication. I mean, how that effects a person is individual because each person probably isn't exactly alike chemically and makeup wise but that's true generally across the board for medicine; right?

A. Well, it may well be different and I think we have a lot of reasons to think it may be different for this concept of addiction because we have this extraordinary experience of treating large numbers of patients with opioids for long periods of time who don't become addicted.

Q. Okay.

A. And, so the use of opioids in the

setting of treating patients with chronic pain seems to be different than the misuse of opioids for recreational purposes in an addict population. So, we -- and that begins to say that there must be very powerful individual differences among these groups and these individuals within these groups that allow someone to take opioids for months on end, to have successful treatment of their pain and then to be tapered off their drug and that's the clinical experience.

Q. The clinical experience you are referring to is in cancer pain patients?

A. And in chronic non-malignant pain patients.

Q. And the chronic non-malignant pain patients you are talking about, the experience, the documented experience, that is what?

A. In groups of patients who develop an acute herpes zoster that go on to develop post herpetic neuralgia and then improve, in patients who have post surgical pain syndromes that are not related to their cancer but occur in the cancer setting that go on for six months or nine months and then improve and they taper off their

drug.

Q. I am talking about -- I am sorry, are you finished?

MR. HOFFMANN: Go ahead and finish your answer.

THE WITNESS: I am talking about patients who have a variety of surgical procedures on their knee or hip or have traumatic pain who take opioid analgesics during their rehabilitation and then recovery and then go off their drugs.

BY MR. COLANTONIO:

Q. And, what I would like -- can you define for me the published studies you are talking about that embody that?

A. Of those patients, those I am speaking of from my own clinical experience.

Q. I understand that. What I am trying to ask you is where could I look at, what body of published literature can I look to to find this, any published experience besides your clinical experience?

A. Right.

Q. If you can define that for me?

A. Yeah, I think we published a paper on

the types of patients that we saw in our pain clinic. And we defined them in like three categories, a group of patients who escalated their drugs, there are a group that remained stable and there was a group that decreased their drugs. So that would be one population that I could identify.

Q. I am sorry, where was that published?

A. I need to look at my --

MR. HOFFMANN: Go ahead.

MR. COLANTONIO: Sure.

THE WITNESS: And, it would be early on. It's number 23 on my bibliography. It's Canner Foley, patterns of narcotic drug use in a cancer pain clinic.

BY MR. COLANTONIO:

Q. And that was published in what year?

A. It was published in 1981.

Q. So, that would have been published at the time you published this article that we are looking at?

A. No, this article was 1985.

Q. I thought you said 1981?

A. I said 1981 and this article is 1985.

Q. That's my point. The article that you

referred to in your bibliography just now was already published at the time you published this article in 1985?

A. That is correct.

Q. True?

A. Yes.

Q. Any others?

A. I think I really would need to think about that for you.

Q. There are none others that you can think of right now if I was to ask you for --

A. Other published studies of that particular point?

Q. Yes.

A. No, not that I can think of at the moment.

Q. In your -- on page 184 at the bottom here, it is like the second to the last sentence --

A. Okay.

Q. You say, given the paucity of data, however, this course must be pursued cautiously?

A. Yes.

Q. I would like to ask you what you meant by the paucity of data, what paucity of data are

you referring to?

A. Well, let me read what I said in this.

Q. Sure.

A. Okay, the paucity of data that we were referring to was the limited studies of patients with chronic non-malignant pain who had been treated with opioids in the literature, the published studies.

Q. In terms of their --

A. The experience of clinicians with it. So we cited the article by Tennant. We cited an article by Taub and we researched the literature to find other examples. And so by paucity, we were concerned about the paucity of patients. So, Taub was an example.

Q. I think you also cited --

A. Sternbacks, Taub, Tennant.

Q. You cited also --

A. Turner, so those are people that had published.

Q. You cited Porter & Jek, footnote 38, do you see that?

A. Yes.

Q. And, you cited that as one of the I guess pieces of data out there?

A. Right.
Q. But, even in citing that and some others, you agreed at the time that you wrote this, that that still constituted a paucity of data at that time --
A. Yes.
Q. -- on these issues; is that correct?
A. Yes.
Q. Now, it says here in the next sentence, long term prospective studies of pain patients on opioid maintenance therapy are needed. And were you suggesting that the long term studies were needed to correct the paucity of data that you were referring to in the previous sentence?
A. Well, they were needed for many different reasons, not just to correct paucity of data. They were needed to help us understand the issues.
Q. Is that one of the reasons?
A. Yes.
Q. And, it says here these will better assess the efficacy and risks of the treatment itself and may provide insight into the salient features which predispose to and perpetuate drug abuse?

A. That is correct.
Q. And, when you use the word drug abuse there, does that include sort of as a subset of that, drug addiction?
A. It would, yeah.
Q. Do you believe that the terms addiction and substance dependence are synonymous?
A. The substance dependence is the language used in the DSM four TR and it is used to describe addiction. So for that group, substance dependence and addiction are used --
Q. And, you have indicated --
A. -- interchangeably.
Q. I am sorry, are you finished?
A. They are used interchangeably.
Q. And, I think you have indicated you have used the DSM four in your practice before --
A. That's correct.
Q. -- in terms of diagnosing addiction; true?
A. Correct.
Q. And, would you also agree that psychological dependence is also synonymous with substance dependence and addiction?
A. Well, I don't want to -- people use --

every time you use each of these words, you have to define it. And so, therefore, I don't want to say that because I don't know how a person is using it. Some person may use it one way and some person may use it another way.

So every time when someone identifies and uses the word psychological dependence, I want them to tell me what they mean. When they say addiction, I want them to tell me what they mean, and when they say substance dependence.

Sadly, it would be good in the field if we all sat down and agreed on these definitions. So I think I can't answer that in that kind of general sense. It is the content, how is it being used, what are you trying to define and that's the best answer I can give you.

Q. Would you agree that even today there is some disagreement among experts and clinicians as to how each uses the terms addiction, substance dependence, psychological dependence?

A. I think there is and that's why you have to start the conversation with are we all at the same place.

Q. While you believe that patients should be individually assessed when they are treated

with OxyContin or opioids, don't you agree with me that individual assessment is true in every case when a medication is prescribed to a patient?

A. I guess, yes, they need to be individually assessed no matter when they receive a medication.

Q. And, you believe that there are certain things in the assessment, especially with opioid medication, that are important including a person's background -- we talked about social factors, economic factors, psychological factors that might play a role in the person's pain and potential for addiction; true?

A. But, I would think that if you were using anti hypertensives or anti depressants or anti anxiety drugs or antibiotics, I would need to know those pieces of information.

Q. So pretty much the kinds of things you would assess in terms of looking at somebody, whether you are going to prescribe them OxyContin or anti -- or a hypertensive drug, you would pretty much do the same kind of assessment?

A. Yes.

Q. So, you would do that for a hypertensive

drug, antibiotic, opioid, pretty much across the board; is that true?

A. That is correct.

Q. So, while there is individual assessment you believe for patients being prescribed medications, the commonality in all of that is that when a physician considers a prescription for a patient, they have to do that assessment for every medication they write; correct?

MR. HOFFMANN: Object to the form of the question.

BY MR. COLANTONIO:

Q. Do you understand my question? In other words, the assessment is common with any drug?

MR. HOFFMANN: I am going to object to the form of that question too, but if you can answer it, go ahead.

THE WITNESS: Well, you need to measure the blood pressure if the patient is -- if you are using anti hypertensives. You need to measure the blood sugar if you are using insulin. I mean, there are very specific assessments that go with each of the drugs as well that are specific. So there is a general and then there is a specific. So for

each class of drugs, there would be a specific assessment as well.

BY MR. COLANTONIO:

Q. But, it is common to all patients that there is an assessment done for a drug before it is prescribed?

A. There is an assessment made that is directly influenced by that drug. So you would ask a series of factors about food intake and glucose intake for someone you are prescribing insulin to.

Q. But, my question is, you agree that is common to all --

A. I would not ask every patient about their food intake if I was not prescribing insulin.

Q. I understand that but what I am saying is I know there are specific nuances to each different medication because there may be different conditions you are treating. My question I am asking you is, the assessment itself, that the physician does the assessment, it is common to any medication, the fact that you do an assessment?

A. It's not so much common to every

medication, it is common to the doctor patient relationship and the setting in which you are caring for the patient.

Q. All right; now, is it your belief today on August 28th or something like that, 2004 --

MR. HOFFMANN: 27.

MR. COLANTONIO: Thank you, 27, 2004 that the use of opioid analgesics such as OxyContin by physicians for the treatment of patients with acute pain is inadequate?

THE WITNESS: Would you repeat that for me?

BY MR. COLANTONIO:

Q. Sure. Is it your belief today, August 27, 2004, that the use of opioid analgesics like OxyContin by physicians for the treatment of patients with acute pain is inadequate at best?

MR. HOFFMANN: I am going to object to the form of the question. But if you can understand it, you can answer it.

BY MR. COLANTONIO:

Q. Do you understand that?

A. Could you say it one more time and I am not trying to be difficult.

MR. HOFFMANN: Say it one more time.

THE WITNESS: But, I am just --
BY MR. COLANTONIO:
Q. It's going to be easier if I just show you your expert disclosure and ask you to take a look at this phrase that was used in it. This way there is no -- I won't botch the sentence and I will just show it to you. There is a sentence right here on the third bullet point.
A. Okay. Yes, okay.
Q. If you could take a look at that, I will pass it over to you.
A. Thank you.
Q. You can read that.
A. The use of opiate analgesics by physicians for the treatment of patients with acute or chronic pain remains inadequate at best, yes.
Q. And, you believe that is true even as of today?
A. I do, yes.
Q. So, I am going to rephrase it a little bit differently but I think it is the same question. So it is your belief that the use of opioid analgesics such as OxyContin by physicians for the treatment of patients with acute pain is

inadequate at best?

A. Well, I would drop out OxyContin because in acute -- OxyContin is not a drug that is commonly used for acute pain.

Q. Do you believe OxyContin is appropriate for use by physicians for patients with acute pain?

A. The indications are for patients who have pain that is going to last more than several days and that requires continuous dosing and acute pain may not require that.

Q. Well, in fact, it says extended period of time, I think now, doesn't it? Do you know what the package insert says for OxyContin?

A. I don't know, I would have to look at it.

Q. OxyContin when it was first promoted, first came out, as I understand it, had in the package insert, the indication of pain lasting more than a few days. Do you recall that at all?

A. I have heard that, yes.

Q. Do you know whether that has been changed?

A. I think it was changed to be for continuous use of a controlled release, need for

continuous administration but I would need to look at it.

Q. If I were to say to you --

A. To be fair to you, I would need to look at it.

Q. If I were to say to you that the indication for a drug was that the pain had to be for an extended period of time, what would that mean to you, an extended period of time?

A. More than -- several days or more.

Q. Would you associate that more with chronic pain than acute?

A. I would.

Q. The phraseology, extended period of time, you would associate more with chronic pain than acute pain; is that right?

A. That is correct. However, there are patients that have -- this gets into the definition. If you say chronic pain is greater than three months, then there are patients with acute pain that have it for three months, and OxyContin would be appropriate if a patient was requiring medication for three months. So again it depends on the definition of acute and chronic pain.

Q. A lot of definitions?
A. Yeah. No, it does.
Q. And, the next thing here, we talked about this already, there is confusion among physicians and patients about what is meant by physical dependence and addiction in that you believe it attributes or causes some fear among people --
A. Yes.
Q. -- for using opioid drugs; right?
A. Yeah, um-uh.
Q. Now, physical dependence, is it your belief that something happens physiologically to the body to cause the body to need and become physically dependent on the drug?
MR. HOFFMANN: I object to the form of the question, you may answer it.
BY MR. COLANTONIO:
Q. Do you understand my question?
A. It's not a matter of opinion. There are a variety of scientific studies that it demonstrated that exposure of receptors to opioids lead to changes in their cyclic AMP which lead them to then cause a variety of effects when the drug is withdrawn.

Q. So, when I take the drug, if I develop physical dependence, then something happens chemically to my body that makes my --

A. Well --

Q. Sorry.

MR. HOFFMANN: Go ahead and finish your question.

MR. COLANTONIO: Thank you.

MR. HOFFMANN: I was cautioning her not to answer your question before you finish it.

MR. COLANTONIO: I probably lost my train of thought.

MR. HOFFMANN: I am sorry, maybe I should just sit on my hands, but --

MR. COLANTONIO: I don't want you to sit on your hands.

THE WITNESS: Sorry.

BY MR. COLANTONIO:

Q. It's your belief that the person who becomes physically dependent, takes a drug, there are physiological changes to their body that make it such that if the drug is withdrawn that the body will react adversely or in a way that comes about because of these physiological changes?

A. Yes.

Q. Now, do you believe that there are physiological changes that happen to the body upon ingestion of a drug that are a contributing factor to the development of psychological dependence or addiction?

A. There is no clear correlation between physical dependence and addiction.

Q. Is what you mean by that that people who are physically dependent, just because they are physically dependent does not mean they are addicted?

A. That is correct.

Q. But, my question is a little bit different, I think, and that is do you believe that in terms of psychological dependence or addiction, that there is something, that there is a physiological mechanism to that, to addiction and psychological dependence?

A. The evidence would suggest that there are a series of neuro pharmacologic changes that occur within the brain with exposure to opioids that are associated with psychological dependence.

Q. So, that would also, I think, mean that in terms of psychological dependence and

addiction, there are something physiological going on that --

A. I am attempting to be specific by calling them neuro pharmacologic because they happen in the brain predominantly.

Q. A person who has addiction can have physical dependence as well; is that right?

A. Can you say that again?

Q. A person who has psychological dependence or addiction to opioids can also have physical dependence, right?

A. Yes, correct.

Q. A person who abuses opioid medication, prescription or otherwise, that can be an indication of potential addiction; is that true?

A. Potential, yes.

Q. And, in terms of differentiating whether somebody has true physical dependence, true psychological dependence or addiction or just drug abuse problems, would you agree that to sort those things out, that one should evaluate the patient and try to figure out which one or a combination of those might be at issue in a patient?

A. That is correct.

Q. Would you expect to see a higher rate of addiction in a pool of patients that have both higher dose of opioids such as OxyContin and longer use of the drug?

A. You know, I think that's the million dollar question. We don't know the answer to that.

Q. Would you expect to see a higher rate of addiction in a pool of patients who have certain, a certain subset of socioeconomic psychological factors than another subset?

A. Again, that's been looked at and not clearly well defined. I think that one of the important issues in all of this is that merely exposure to opioids does not produce addiction. And so trying to sort out what those factors are is the -- is an important aspect.

There is evidence to suggest that patients who have a history of alcohol abuse or have a history of drug abuse may be at greater risk. But, these are very limited information.

Q. That's the $2,000,000 question?

A. Yeah.

Q. All right; in terms of history of alcohol abuse, let's say that you have a patient,

comes into your offices, and they want to -- you are considering OxyContin as a potential drug, and you take a history of a patient. If a patient had gotten drunk socially, let's say, I don't know, once every three weeks or something like that in the past year, would you consider that a history of alcohol abuse?

A. There are different criteria that you can use to assess a patient. And, you know, this has been well described as to whether they binge or whether they take five drinks a week, etcetera. So there is an assessment that one can do of a patient. But there are a couple of studies out there that begin to look at this.

Nat Katz looked at a group of patients with chronic opioid therapy and demonstrated that those patients that had a history of alcohol abuse did fine in his clinic and did not develop any risk of addiction. And, Edwardo Bruera in a large population of cancer patients used alcohol abuse as one of the factors that you might evaluate the success of pain treatment in a cancer population and he eventually threw out alcohol abuse because it became a variable that wasn't helpful.

Q. But this Katz and is it Bruera, are they recent studies or --

A. Katz is a recent study. It's a really nice piece and I can get you the reference. I don't have it with me, but it's really -- I forget who wrote it with him, but it's a nice piece.

Q. Now, we're going to get into definitions again. What is recent?

A. In my world, recent is like the last three years or four years. And Edwardo, I would have to see where he published that but the Katz papers were recently published.

Q. Now, let's talk about history of drug abuse.

A. Yes.

Q. If somebody had smoked, let's say, marijuana in college or something like that, would you consider that a history of drug abuse in your evaluation?

A. Yeah. It would be written down as a history of drug abuse, yeah.

Q. And, would you think that kind of a person would be -- fall into that category of maybe the higher risk of potential addiction to

some others?

A. I don't think we have any information on that.

Q. That falls into the paucity of data --

A. That alone, you know.

Q. That would fall into the paucity of data column?

A. You know, I don't think I know the answer to that because I don't -- there may be research that has looked at marijuana and its implications, I just don't know it.

Q. Do you in your own practice consider a history of drug abuse like somebody who smoked marijuana in their past or maybe abused a drug, prescription medication, took it more than was prescribed, do you consider that an additional risk factor for development of addiction when you are considering prescribing an opiate?

A. I consider it as an important piece of information. And, you know, again, I don't want to discriminate against the patient who may in the past have misused drugs. And so in that setting, it's a piece of information that you want to have information about the patient on and information to what the causes of why they did

it, how they did it, whether they continued to do it, what they think about it. And also the very fact that the patient is open and willing to tell you that in an interview suggests that it may not be at all an issue.

And, when you have to weigh the risks and benefits of treating a patient, it is a dilemma that you face, a very real dilemma. So, yes, it's a piece of the history that you put, it's the piece that you pay attention to and in that patient, it might represent a greater concern or a red flag.

Q. It could be something that would make you consider not prescribing OxyContin for somebody, depending on how you felt about it; correct?

A. Well, I think, again, I don't -- it could make some people make that decision. But I would hope that they had more information and weighed the benefits to the patient of treating their pain than the risk of the drug.

Q. That's pretty much true every time a physician writes a prescription, that's kind of a risk benefit, you want to make sure that the drug is not going to cause more damage than --

A. More harm to the patient.
Q. In fact, that's kind of the concept of physician practice, don't cause harm and don't -- isn't that true?
A. Yes, it would be that.
Q. Do no harm, I think I have heard that before?
A. But, I think particularly when you see a patient writhing in pain who is profoundly suffering, that is rather compelling than simply looking at a blood pressure number or looking at a cholesterol level, it's quite profound.
Q. Especially in cancer pain patients?
A. No, I think it's even sadder in patients that don't have cancer because they may not die and they may have to live with it.
Q. If a patient has terminated opioid medication and they have developed addiction, there could be a reason for continued management of that patient, is that correct?
A. Well, could you say that again?
Q. Sure. If a patient has stopped opioid medication but the patient has developed psychological dependence or addiction, there could be a potential reason to continue to treat

that patient?

MR. HOFFMANN: I am going to object to the form of the question but you may answer if you can.

BY MR. COLANTONIO:

Q. Due to the risk associated with addiction --

MR. HOFFMANN: I still object to the form of the question.

THE WITNESS: Well, if a patient is an addict, they are an addict and they are abusing the drug. If a patient has a history of drug addiction, they don't need treatment so I don't --

BY MR. COLANTONIO:

Q. Well, I think you indicated before that if a patient does develop addiction, they could need treatment to treat that condition, addiction, correct?

A. I did and that would be a patient who has, let's say, actively been misusing opioids, is physically dependent on them so they need the opportunity to be detoxified from their drug. They need to be put into any one of a series of programs like a drug abstinence program, a drug

free program, a narcotics anonymous program, a methadone maintenance program or buprenorphine program, okay, for a period of time.

But once they have done that and once they are no longer on the opioids and once they are discharged from those programs which lasts periods of time, they don't need to -- they don't need more treatment.

Q. Don't those programs also often times have periods where patients come back? There can be relapses, there can be additional support provided for the person to deal with this lifelong problem?

A. Well, if the patient has a relapse, then they need treatment for the relapse. But they don't -- if they don't have a relapse, they don't -- they don't have anything they need a treatment for.

MR. COLANTONIO: Let's take five minutes.

THE VIDEOGRAPHER: Going off the record, 10:46.

(Whereupon, a brief recess was taken.)

THE VIDEOGRAPHER: Returning to the record 11:04.

BY MR. COLANTONIO:

Q. Do you agree with this statement, drug addiction is a treatable disease utilizing a multi disciplinary approach but relapse is common?

A. Yeah.

MR. COLANTONIO: Those are all the questions I have.

MR. HOFFMANN: Why don't we see if the people on the phone have questions.

MS. SEAMON: I don't have any.

MR. FARRELL: Bob Farrell, I have none.

MS. DOBBINS: This is Stephanie Dobbins, I have no questions.

MR. HOFFMANN: It is our hope that Dr. Foley will testify live. But in case that turns out not to be possible, I am going to ask some questions on direct.

MS. LYONS: Are you going to be doing that from there, Bill?

MR. HOFFMANN: No, I was going to suggest that I switch seats so that she is looking into the camera when she is responding to me.

THE VIDEOGRAPHER: Going off the record,

11:05.

DIRECT EXAMINATION

BY MR. HOFFMANN:

Q. Dr. Foley, I just have a few questions for you. First, when did you receive your medical degree?

A. In 1969.

THE VIDEOGRAPHER: Returning to the record, it's 11:09, beginning of tape number three.

MR. HOFFMANN: I'm sorry, I beg your pardon.

BY MR. HOFFMANN:

Q. Dr. Foley, when did you receive your medical degree?

A. 1969.

Q. And, do you hold any board certifications?

A. I am board certified in neurology and psychiatry.

Q. And, when did you become board certified in neurology and psychiatry?

A. 1975.

Q. How would you describe your specialty in the field of medicine?

A. I was trained as a neurologist and then as a neuro oncologist and then as a clinical pharmacologist. And I work at Memorial Sloane-Kettering Cancer Center and my focus has been on the clinical pharmacology of opiate analgesics in patients with pain.

Q. How long have you been focusing on the clinical pharmacology of opioid analgesics in the treatment of pain?

A. Really, since I finished my residency since 1974, when I went to Memorial.

Q. Have you prescribed opioids to patients since 1974?

A. Yes, I have and before that as well as an intern and resident.

Q. And, over the course of your practice, can you give me any kind of estimate as to how many patients you have prescribed opioids to?

A. Thousands of patients.

Q. And, do you continue prescribing opioids to patients today?

A. Yes.

Q. Have you -- in prescribing opioids to patients, do you see any advantages to long acting or sustained released opioids compared

to on the one hand, compared to short acting or immediate release opioids on the other hand?

A. Well, for patient's convenience, it has had a very important impact because instead of having to take a medication every three hours or four hours, they can take it every eight hours or 12 hours or in some cases every 24 hours because there is a series of preparations out there that allow them that kind of variability.

Q. Did you have anything to do with the development of sustained release opioids?

A. In the late seventies and early eighties, there was an increase in attention to the role of oral morphine in patients with pain and cancer. And after there was available oral morphine in an immediate release, there was an increasing interest by a variety of companies to develop slow release or controlled release preparations. And so we worked with a variety of companies in developing slow release and controlled release preparations for Morphine.

Q. When you say we worked with a variety of companies, just what did you do?

A. My particular role was in advising the companies about who had cancer pain, who would be

appropriate for studies, what the study designs might be, those particular aspects.

Q. Did you have anything to do with the encouragement of the pharmaceutical industry to develop a sustained release morphine?

A. Yes, because we felt that patients would benefit from drugs that would facilitate their ability to have continuous pain relief. So, we were encouraging to the pharmaceutical companies I guess would be the best.

Q. Now, I want to understand a little bit about your patients because, as I understand it, you work at a facility that specializes in the treatment of cancer. Would it be fair for us to assume that all the patients you treat have pain from cancer and will be on opioids until they die from that cancer pain?

A. No. Again, when we started, since we were clearly -- the clinic was called the Medical Pain Clinic. It was initially developed by Gray Hood and it became -- in it we saw a wide variety of patients with both cancer pain and non-cancer pain.

Q. Have you in your professional experience ever prescribed opioids to patients for pain and

then had that pain, the pain -- the cause of the pain resolve and you wean the patients off of opioids?

A. In our setting, it has been a very common phenomenon to see that, both in the group of patients who have prolonged post surgical pain syndromes that last weeks or months, patients who have prolonged orthopedic procedures and patients who have, for example, neurologic pain syndromes like brachial avulsions of the brachial plexus or have post -- acute herpes zoster that then goes on to post herpetic neuralgia. And there are groups of patients who for a period of time take opioids and then are tapered off the drug because they are rehabilitated, they are improved, their pain dissipates and they are no longer taking them.

Q. I asked you about patients that you had prescribed opioids to but are you also familiar with patients that fellows in your program provide opioids to?

A. Since 1975, we have had a training program and, you know, Dr. Portenoy, Dr. Paine, a whole variety of individuals who now are experts in this area have trained in our program.

Q. Now, of the patients that you are familiar with through your treating them personally and supervising your fellows in treating them, what percentage of patients do you find are successfully weaned off of opioids when their pain issue resolves and then subsequently become opioid addicts?

MR. COLANTONIO: I am just going to object to the form of the question and also object on lack of foundation.

BY MR. HOFFMANN:

Q. Doctor, go ahead and answer it.

A. Could you repeat the question?

Q. Yes. Of the patients to whom you prescribe opioids and to whom your fellows prescribe opioids, what has been your experience in terms of patients who have been prescribed opioids, then weaned off of the opioids when their pain issue resolves and then at some subsequent time become opioid addicts?

MR. COLANTONIO: Same objection.

THE WITNESS: That has not been part of our experience. We haven't seen that occur in our patients. The patients have been tapered off their drug successfully and

unless they have a recurring pain problem which they may go back on their drug, that may occur, but we haven't seen them develop any problems with just having been exposed to the drug as part of a surgical procedure or prolonged post surgical procedure or as part of any other cancer illness or non-cancer illness.

BY MR. HOFFMANN:

Q. Well, would you know if they did?

A. Well, again, because these patients often are in a setting of a cancer institution, we would see them because they may come back to our institution if they had a relapse and might have abhorrent behaviors. They would typically come back to us because, and we would know about them because the physicians who may be treating them would want their records for what had happened to them in the past. And those records requests would come directly to our program. So, we would tend to have a sense of who they were.

MR. HOFFMANN: I want to mark this as an exhibit.

(Whereupon, Defendant's Exhibit 1 was marked for identification.)

BY MR. HOFFMANN:

Q. Dr. Foley, we have handed you what has been marked as Defendant's Exhibit No. 1 and I will represent to you that that is an exhibit to the deposition of Edon Nelson that has been taken in this case. Is that a document that you have reviewed previously?

A. Yes, I think I have.

Q. I want to ask you a few questions about that. Specifically looking at paragraph one and the last sentence of paragraph one, it states, however, it is standard medical practice to avoid the use of opioids for persons suffering long term non-traumatic moderate levels of pain because continued pain management can only be achieved over time by increasing the dose of the opioid prescribed. Do you agree with that statement, Dr. Foley?

A. No, I don't agree with that statement.

Q. Why not?

A. Well, again, it would be helpful to take it in different pieces or parts. First of all, now, it's been recognized that there are -- there is a sub group of patients who may respond effectively to opioid analgesics on a chronic

long term basis and they would be potential candidates. And, again, there have been a variety of studies that have demonstrated the efficacy of opioid analgesics in patients with neuropathic pain and different types of arthritis pain and in patients with low back pain and patients with post herpetic neuralgia and patients with peripheral neuropathy. So there have been now guidelines written by the American Pain Society and the Academy of Pain Medicine to identify that such patients may benefit and should be considered for treatment. So, that's my sort of first part.

I disagree with that the construct that continued pain management can only be achieved over time by increasing the dose of opioids prescribed and I disagree with that statement because even our very small study of the 38 patients that we talked about previously demonstrated that those patients did not necessarily escalate their drug.

And, again, there is increasing evidence that patients can stay stable for long periods of time on chronic opioid therapy.

Q. Let me ask you a little bit more about

that because it is my understanding that Dr. Nelson has opined that because of the development of tolerance, there is no plateau that patients reach and a patient prescribing opioids will continue to need escalating doses of opioids as the tolerance to the opioid increases. Has that been true in your experience?

A. It's not been true in our experience or in others in which this conceptualization of tolerance which does develop in some patients, the development of tolerance per se has been hypothesized to be the driving force for why patients require higher doses of drugs. And yet when one looks at it in a population of patients, one sees that it's typically the change in the pain stimulus that is driving the requirement for an increase in the drug.

And so the animal studies that are the basis for this whole understanding of this phenomenon were done in which the stimulus was kept the same. When you change the stimulus as occurred in patients, the reason for them increasing their dose of drug is then escalating pain or progression of disease.

So, the bottom line to all of this is that tolerance occurs to different effects of the drug at different rates, that many patients can take a stable dose of drug for a long period of time and there is literature to support that and so that they don't just increase their drug continuously but rather stay at a stable dose.

Q. Can you recall any examples of patients that you have had that have been on a continuing non-escalating dose of a particular opioid for over a year, for example?

A. I mean, I have a series of patients like that. I have a woman who is an 85 year old patient who takes oxycodone and has been taking exactly the same dose for relatively -- has been taking -- she has been taking 240 milligrams of oxycodone for now five or six years for neuropathic pain syndromes. And she lives independently and lives here in the city and her daughter lives in the same building. And I see her on a regular basis and she has not escalated her dose of drug, as an example.

Q. Has this impaired her cognitive function?

A. No, she is fully independent, has been

able to live independently.

Q. In your experience, does being on a continuous high dose of opioids such as you described for this patient, impair a person's cognitive functioning?

A. It potentially could but our experience, again, is that patients become quite tolerant to the side effects that impair cognitive function so that they are tolerant to the sedative effects and they are tolerant to the somnolent effects and they are tolerant to the confusion effects of the drug so they remain stable.

Q. And, you mentioned with regard to this patient that she was on oxycodone, any particular -- well, was this particular patient on OxyContin?

A. She was not on OxyContin because her insurance company refused to pay for OxyContin.

Q. Do you prescribe OxyContin to some of your patients?

A. Yes, I do.

Q. I would like you to look now at paragraph three of Defendant's Exhibit 1 where it states that it is a well established medical fact that seven percent of all persons chronically

exposed to opioid analgesics will become addicted to the narcotic. Do you agree with that?

A. No, I don't.

Q. Do you know -- do you as part of your practice keep up with the literature on opioid addiction?

A. Yes, I do.

Q. Are you aware of any support in the literature on opioid addiction that would support that statement in paragraph three?

A. I don't know of any data that would support that. I mean, all the data that I know of says that we don't know this number.

Q. What if we change that number to three and a half percent, what would your answer be then?

A. I would still say that we don't know the number.

Q. There is a statement in the package insert that says in effect that addiction to opioids when prescribed for pain is rare. Do you agree with that or disagree with that?

A. Yes, I agree with that.

Q. What is the basis for your agreement with that?

A. First of all, it is my only clinical experience in treating patients with pain. And, again, this has been the evolution of having the opportunity to be able to provide chronic opioid therapy for patients for years at a time and to see how rare this phenomenon is in that patient population. So, that's one basis. And, increasingly, that of my colleagues who have also observed this.

And then when Dave Durrenson looked at the relationship between increasing prescriptions of opioid analgesics and increasing the abuse from like 1990 to 1996, he demonstrated that there was no evidence of abuse. And this is again looking at that same period.

So there is a series of suggestions that have identified and an increasing number of patients who are being treated with opioids that have begin to question whether anyone in the setting of receiving opioids in the setting of pain becomes addicted. And it is really I think such a critically important question because the experience of caring for patients and treating pain in a medical setting is just totally different than what we see happens in addicts who

take this drug and misuse it.

Q. Let me ask you to turn over to paragraph 12 on page 4 of Defendant's Exhibit 1, if you would, please? In looking at the first sentence there, it states, the duration of analgesia from OxyContin falls short of the 12 hours published in the package insert. Do you agree or disagree with that?

A. I haven't reviewed all of the pharmacokinetic data so I don't think I could even agree with that statement because I don't know that that statement is true. So --

Q. In your experience as a treating physician, has the duration of analgesia from OxyContin fallen short of the 12 hours published in the package insert?

A. Again, in treating patients, you have to choose the appropriate dose. So, if you -- the time action of a drug will be directly related to the dose you give the patient. So, if you end up under dosing the patient, then they may have inadequate analgesia and look like the drug doesn't work for 12 hours.

So, I have a lot of respect for how the FDA reviews this pharmacokinetic data in deciding

whether a drug works for what period of time because they are very very stringent about that. So, my sense is that typically you have to give the patient the appropriate dose.

Q. If a patient is on active opioid therapy, is there any obligation on behalf of the treating physician to monitor that patient to determine if symptoms of addiction begin to occur?

A. Yes, of course.

Q. If a patient has been on opioid therapy and has successfully weaned off of the opioid, is there any reason to continue to medically monitor that patient for the rest of his or her life to determine if that patient will become an opioid addict?

A. I mean, there is no, no indication to do that and there is a lot of clinical data to suggest that we would not do that.

Q. Let me ask you now to turn to paragraph 13 beginning on page 4 and continuing on page 5 of this, the Exhibit 1, Defendant's Exhibit 1. And it's fairly long so I am going to ask you just to read that paragraph to yourself and then I would like to ask you what you agree with and

disagree with in that paragraph?

A. So to start with reading paragraph 13?

Q. Yes, just read paragraph 13.

A. I don't agree with what it says.

Q. Well, why don't you go through the paragraph and take it any way you want, sentence by sentence, if you would prefer, and explain why, tell us where you don't agree and why you don't agree?

A. Well, patients have used OxyContin and have then discontinued the OxyContin and then their pain has improved. They no longer require taking the drug. There would be no reason to monitor them for anything other than general medical care. So it would not seem to me that you would monitor them for anything related to OxyContin.

Then this issue, exposure to large dose, i.e., more than 30 milligrams per day, I don't know of any evidence that, first that someone would call 30 milligrams large doses. Second of all, that that dose would produce these particular effects. It may have some effects that would be the foundation for addiction.

30 milligrams per day at least in the

published studies and I think it's up to -- I am not quite sure, it's up to 60 milligrams, patients could be abruptly stopped from their drug and not even go into withdrawal. And this was noted in a chronic long term study that was published in patients receiving opioids for osteoarthritis. So we have evidence that even up to 60 milligrams when a patient was stopped, they didn't even show signs of physical dependence.

So I don't know the basis, any scientific basis for that dose of 30 milligrams. So, to suggest that all persons have been exposed to sufficient doses for a sufficient time to produce a basis for addiction, I don't know of any understanding or any basis and it clearly is not within my clinical experience.

Then this sentence, euphoria is produced from relief of pain. Well, every bit of data shows that euphoria occurs independent of an analgesic effect if it occurs. And again in the oxycodone, OxyContin studies, euphoria was reported to occur in somewhere between one to five percent of patients as a side effect. So a very rare complication compared to the complications, the side effects that we have

reported.

So this construct of euphoria having -- the idea that euphoria is related to pain is incorrect, number one. And that it occurs as a result of oxycodone is a rare phenomena.

Oxycodone is metabolized to oxymorphone but the data demonstrates that there is the major active ingredient is oxycodone in producing the analgesic effects. Then this idea that it is remembered and leads to a desire to repeat the drug administration, well, it is not even remembered enough to produce physical dependence which is often closely associated with drug addiction.

So, it would seem to me unlikely that there would be any clear relationship there. I agree with the statement that intense drug craving is a hallmark of opioid addiction.

So, in short, I don't know of any evidence to suggest that if somebody has been exposed to 30 milligrams of oxycodone that they should be followed -- OxyContin, that they should be followed for the rest of their life. And there are a lot of patients in a post operative setting who receive oxycodone which is the active

ingredient of OxyContin who sure are not being followed for the rest of their life and have no problems with addiction. So I don't think there is a basis scientifically or in clinical practice.

Q. You were asked some questions about your CV or articles in your CV earlier this morning and just for the record, I would like to mark and include as an exhibit the CV that you were asked about.

And let me just ask you, it appears that the most recent publication on this, if these are in fact in chronological order, is 2001 --

A. Yeah, that's wrong.

Q. And, we can substitute another CV at a later date. But my question is, as of August, 2001, is this an accurate curriculum vitae for you?

A. Do you want me to look at every page?

Q. No, just see if you recognize it as your CV.

A. I do recognize it as my CV but we keep addressing -- it may not be fully updated.

MR. HOFFMANN: Okay; then let's mark it as Defendant's Exhibit 2 and make it part of

the record, then?

(Whereupon, Defendant's Exhibit 2 was marked for identification.)

THE WITNESS: Okay; and it clearly isn't updated since it's 2001.

MR. HOFFMANN: Let's take a break for just a minute of minutes.

THE VIDEOGRAPHER: Going off the record 11:36.

(Whereupon, a brief recess was taken.)

THE VIDEOGRAPHER: Returning to the record 11:40.

BY MR. HOFFMANN:

Q. Dr. Foley, I just want to try to clarify one more thing from your testimony this morning and that is the distinction between a weak opioid and I guess a strong opioid.

A. That is correct.

Q. And, in the case of some opioids, does the distinction between strong and weak depend on dose?

A. Yes and no, but in drugs that are pure agonist like oxycodone it is an issue of dose.

Q. Okay, well, let's stick with oxycodone. Is it a hard and fast distinction or is it a

continuum between strong and weak.

A. It's been traditionally a way in which drugs as they came on the market from about the 1950s on were categorized as to what was thought to be their spectrum for analgesia. So, let's say codeine has been considered sort of the prototic drug so doses of 30 or 60 milligrams of codeine were identified as weak opioids and then were studied in patients with mild to moderate pain.

Q. Is OxyContin identified generally as a weak opioid or a strong opioid?

A. Well, I think -- OxyContin, it is a brand name. The agent is oxycodone and so I think we just have to talk about oxycodone. And oxycodone at low dose like five milligrams, ten milligrams is considered a weak opioid. And because of that consideration is why it was placed in the WHO step two analgesic ladder at step two and then it was placed in step three at higher doses.

Q. And, is there a hard and fast line where you draw the distinction between higher doses and lower doses when you are talking about oxycodone?

A. Again, it's not a hard and fast line but

it's clearly doses of five milligrams or ten milligrams have been considered low dose and at a step two ladder.

Q. And, doses above that have been considered strong opioids?

A. No, I am identifying those for sure and above that again is quite individual. So, to be fair -- and I think I would have to go back and look this up -- but I think it would go up to about 30 milligrams would consider it still in a weak opioid class.

Q. 30 milligrams daily?

A. Yes.

MR. HOFFMANN: Those are all my questions, thank you very much.

Now, Mr. Colantonio may have some more or may not.

MR. COLANTONIO: I do have a few questions, doctor.

REDIRECT EXAMINATION

BY MR. COLANTONIO:

Q. Doctor, in terms of the dosing of OxyContin at Q 12 and the issue of the efficacy of OxyContin over Q 12 over versus Q eight, are you aware of any statistics that would indicate

the number of physicians who prescribe OxyContin who actually write it at Q 8 versus Q 12?

A. I think in one of the many depositions that I read, I read that there was IMS data that suggested that some percentage, 14 percent or something like that, I really would need to look at exactly what they said, wrote the drug Q eight hours.

Q. And, would you consider, if that's true, 12 to 14 percent of physicians write OxyContin at Q eight and not Q 12, would you consider that statistically a significant number of physicians?

MR. HOFFMANN: I object to the form of the question.

BY MR. COLANTONIO:

Q. Do you understand what that means?

A. I don't understand what that means.

Q. Do you understand what the term statistically significant means?

A. As compared to what?

Q. As compared to -- in your profession, do you understand what the term statistically significant means?

A. Well, I would have to have all the data

to make that -- I don't know what the P value is so what P value are we talking about.

Q. What do you mean by P value?

A. That's the degree of significance. So you would have to have all the data to call that significant.

Q. So, if you're trying to assess how many physicians write a drug at Q 8 versus Q 12 and you find out that 12 to 14 percent do that, would you consider that a significant number of physicians?

A. I would consider that a relatively small number.

Q. Do you know the reason why physicians would write OxyContin at Q eight versus Q 12? Have you ever researched that at all?

A. No, and even if they write it, it doesn't mean that that's how the patient takes it.

Q. Well, we hope that a patient takes it how we write it, isn't that right?

A. But writing it doesn't mean that's how the patient is taking it.

Q. Are you aware of any information indicating that patients had related to their

doctors that OxyContin after Q 8 was not working?

A. Um-uh.

Q. Versus Q 12?

A. Yeah, and I think this may be an example of under treated pain of an inadequate initial dose. And so one of the choices would be that you would go up on the dose, you would increase the dose and then expand the time interval. And, we know when you study -- well, there are sort of several aspects of this.

Some patients find that taking a drug on a Q 8 hour basis provides them with adequate analgesia and less side effects. So, they take let's say they take 40 milligrams of OxyContin in the morning and they can get relief for 12 hours. But they notice that for the first three hours they are a litter bit more sleepy than they would like to be and then they are fine.

But if they take 20 milligrams every eight hours, they don't feel so sleepy in those first three hours and their side effects spectrum is less. And so it is more acceptable to them to function at the way that they need to function to take it on a Q eight hour basis. And this reflects the individual variations of patients as

they take drugs.

And we have learned this with transdermal fentanyl, we have learned this with slow release morphine preparations, that you may have to adjust it for some patients, the time frame of using controlled release preparation because it is the best way to minimize their side effects.

So, there is a need to be that type of flexibility and to prescribe that for some patients.

Q. If you were to learn that a significant number of patients reported that OxyContin was not working for them relieving their pain beyond Q eight, would that be a potential indication for you that OxyContin was not being effective after Q eight?

A. It's very possible but not being effective would not be the information I would need. I would need a lot more. I would need to know what their side effects were. I would need their dose. I would need to know whether their dose was matched to their prior narcotic exposure. So you would need to know all of those pieces. But, in my experience, we often have to

change the interval on how we manage the patient's pain based on the individual needs of the patient.

And we have done pharmacokinetic studies with all of these drugs which show some patients half-life is four hours and some patients is eight hours and some is 12 hours. So I would have to know the half-life of the drug in that particular patient.

Q. It would be a piece of the information you would consider in terms of determining whether or not the drug is effective?

A. If the patient has reported that, sure.

Q. As far as you were commenting on Dr. Nelson's opinions and one related to tolerance --

A. Yes.

Q. You agree that tolerance is a predictable pharmacologic effect of opioid treatment?

A. I wish it were predictable, it is not predictable.

Q. Let me, if I could, step down the table a minute and I want to show you what was provided to us as your opinions in this case and ask you

to look at the bullet point towards the bottom of the page. And it says here tolerance and physical dependence are predictable pharmacologic effects seen in response to repeated administration of an opioid in both man and laboratory animals. Do you agree with that statement?

A. Yes and no. I think -- I wish I could predict it but I will say yes, fine, I will agree with it.

Q. Do you want to change your answer, what you said?

A. No, it's fine, I will agree with it.

Q. So, are you saying that the answer you just gave me a minute ago was incorrect and now it is yes?

A. No, the answer I gave before is that I can't answer it with yes it is predictable, no it is not predictable. It has a series of other paragraphs that would go with it.

Q. Let me ask you this question. Is that statement on that piece of paper correct or incorrect?

A. It is correct.

Q. And, you do agree that tolerance can

develop in patients who are --

A. Absolutely.

Q. And, if tolerance develops, then there is a need to increase the dosage?

A. Well, tolerance to what?

Q. Well, how do you define tolerance?

A. Well, tolerance develops to a wide range of the side effects of the drug. And what again we have observed is that, for example, patients develop tolerance to the respiratory depressant effects of the drug.

Q. I guess what I am referring to is tolerance to the effect of the drug on pain?

A. So tolerance to analgesia.

Q. Yes.

A. So, if a patient has tolerance to analgesia, one would have to increase the dose.

Q. And, tolerance to analgesia is something that occurs to patients on opioid medication like OxyContin; is that true?

A. That's true.

Q. Now, you did indicate that you believed that psychological dependence or addiction to opioids is rare; is that your feeling?

A. That is correct -- is rare in patients

who are medically treated with opioids in the setting of having a chronic pain syndrome.

Q. Do you believe that that characterization rare is dependent upon, could be dependent upon some of the factors we talked about before such as the socioeconomic factors, psychological factors, that it may be for a particular sub group that the potential for psychological dependence or addiction could be greater than rare depending on those factors?

A. Yeah. Yeah.

Q. You also indicated that part of your opinion is based on your own clinical experience and then you mentioned you have treated a number of patients. But have you ever gone back and actually precisely quantified the exact number of patients that you have treated?

A. I mean, I could do that because we kept records of all the patients we saw.

Q. I understand you can do it. I am just asking you if you ever actually have ever done that.

A. At the annual reports at the end of the year we said how many patients we saw.

Q. As you sit here today, do you know how

many exactly you saw?

A. No, I don't think I could give you an exact number.

Q. As far as the number of those patients that were treated with mild opioids versus strong opioids, I presume as you sit here today you can't tell me that exact number?

A. No, but the predominant number of patients would be treated with opioids.

Q. I think my question was strong opioids versus weak opioids, could you tell me --

A. No, I could not tell you that today.

Q. And, would you agree that as of today, you believe the data is not available to establish a true incidence of addiction to opioids. Do you agree with that statement?

A. I agree with it.

Q. I think you indicated that your belief about the rarity of psychological dependence or addiction is based upon some published studies; is that true?

A. There are published studies.

Q. Well, is your belief -- is your statement that you believe psychological dependence or addiction to opioids is rare, is

that based in any way on a study?

A. It is based really quite profoundly on my clinical experience and then it is supported by these clinical studies.

Q. So, your opinion that you have that addiction or psychological dependence to opioids is rare is based upon your clinical experience; is that true?

A. That's correct.

Q. It is not based upon or in forming that opinion, you are not relying upon the published studies concerning addiction rates and opioid treatments; is that true?

A. That's true, simply for the fact that we probably have one of the largest populations of patients who have been treated with opioids in the country so it's a pretty large population.

Q. Now, when you talk about your own clinical experience, you do have patients as you indicate that would come back to you for treatment because they might have cancer disease or some other disease that requires retreatment; is that correct?

A. Retreatment for their pain.

Q. Yes?

A. Um-uh.
Q. Or some physical problem?
A. I guess I don't know what you are asking me.
Q. You are saying that the reason why a patient would come back to you is retreatment for pain; is that right?
A. That is correct.
Q. And, that's one way you indicated that you could gauge whether or not that person was addicted or psychologically dependent upon the drug because you had a chance to reexamine that person in the future after they stopped their medication?
A. I guess so. But the patient wasn't addicted when they left us so -- and, I don't have any evidence that when they are not addicted when they left us, that they come back to us addicted unless they are abusing drugs on the street.
Q. Well, is it possible that a person could have opioid medication, stop that opioid medication and a physician based upon how that occurred believed that the person is not addicted and that person could actually be addicted and

later on manifest the signs of that addiction?

MR. HOFFMANN: I object to the form of the question.

BY MR. COLANTONIO:

Q. Do you understand my question?

A. It's a little complicated.

Q. Is the question complicated or the issue?

A. Well, the issue is complicated but the question is a little complicated so if I could take it in pieces, like the first --

Q. Let me try to rephrase it for you. Is it possible that a person could be on opioid treatment like OxyContin --

A. So it could be -- can I interrupt you? Is this all right?

Q. We will set up the circumstances.

A. So, go ahead. The patient is receiving pain therapy for their pain.

Q. Yes.

A. And is taking OxyContin.

Q. Yes, they are then weaned off OxyContin.

A. So their pain goes away and they are taken off the drug.

Q. Yes, and at that time you believe that they are not addicted to the drug, at the time that their medication is stopped?

A. They have no abuse behaviors, they have no abhorrent behaviors, they have no signs of physical dependence, they have no signs of psychological dependence, they haven't been selling their drugs, I have no evidence of any of that behavior, okay.

Q. Or you have some evidence but not enough to convince you?

A. Say I have no evidence.

Q. Say you have no evidence. Is it possible that that person could still have addiction but it doesn't manifest itself until later on?

A. No.

Q. That is not a possibility?

A. Well, addiction -- if we agree with the definition of what addiction is, they don't have it. They don't have what is addiction.

Q. But, is it possible that -- I mean, addiction is based on to a large extent what a person does?

A. Right, they are not doing it so they

don't have it.

Q. Is it possible that they can do it later on after they leave that treatment and they can be addicted to the drug?

A. But, everything is possible, you know.

Q. I am just asking you if this is possible.

A. No, I would say it's highly impossible but who am I to say. But since everything in the world is possible but then you wouldn't call them addicted, it's -- it doesn't make sense.

Q. What would you call them?

A. Well, if they are addicted, then they have all of the patterns of the behavior. I don't know what to call them. I wouldn't even ever think that this was an issue.

Q. So, to your way of thinking, a person, if they stopped a medication and they don't have the signs of addiction at that point, they can never never be addicted to that drug?

A. Ever in the future?

MR. HOFFMANN: Object to the form of the question.

MR. COLANTONIO: That's fine.

THE WITNESS: They could be addicted to

the drug if they took it another time and something else happened, that could happen. But pure exposure to the drug in the setting of pain is not any reason to say that they could be addicted.

BY MR. COLANTONIO:

Q. But, exposure is a prerequisite for addiction; true?

A. You can't be addicted to the drug if you don't take it. You can't be addicted at the time if you haven't and are not taking it.

Q. So, you need exposure to the drug --

A. At the --

Q. I am sorry, to have addiction?

A. You need exposure to the drug at the time that you are being called an addict.

Q. And, you agree that there is or physical dependence is often associated with addiction; is that true?

A. It is often associated but it is not necessarily has to be part of the definition.

Q. But, it is often associated with addiction; is that true?

A. It's associated.

Q. Now, as far as the WHO step two ladder

--

A. Yes.

Q. You indicated that that -- you said something like that's why OxyContin is on step two, I think. I just want to make sure I am clear about this. You stated in testimony here before we broke before that the WHO step ladder, step one, is mild pain; true?

A. Yes.

Q. And, you stated --

A. Mild, yes.

Q. And, you stated that step two was moderate pain; is that true?

A. Um-uh.

Q. You have to say yes.

A. Yes.

Q. And, step three is severe pain. True?

A. Right.

Q. It would be incorrect to suggest that step two is mild pain; true?

A. No, I wouldn't say that because again as it has been described, no one could tightly categorize and just say mild pain and moderate and severe. So, it was said mild to moderate, moderate to severe. And so if you look at it,

it's this continuum and where does the end of high mild pain enter into the early parts of moderate pain. And that's the dilemma.

So the important aspect is that these drugs were categorized. And that's why we went even further to categorize them as weak opioids versus strong opioids, to recognize that there is this continuum and we can't say that the person at the high end of mild pain reporting it at a four and five isn't really moderate pain and the person who reports a seven isn't severe pain.

So simply that language of mild, moderate and severe is forcing us into a box that is arbitrary.

Q. But, it is a step ladder and it does have labeling to it?

A. It does have labeling to it, right.

Q. Is the labeling step one is mild, step two is moderate, step three is severe or is it that step two is mild to moderate and step three is moderate to severe, which labeling is correct?

A. I think all of the labeling is correct because it's a continuum. It's a continuum.

Q. So --

A. So that when we talk about mild,

moderate and severe, we are talking about intensity of pain. When we talk about the drugs used, okay, then we are talking about non-opioids, weak opioids and strong opioids. And the problem here is I think you are asking me to compare apples and oranges.

Q. I don't want to ask you to compare apples and oranges. I want to stick to oranges and oranges.

A. Okay, me too.

Q. So, is it your testimony then that step two includes mild pain?

A. It could include mild pain.

Q. OxyContin is not indicated for mild pain; true?

A. Again, oxycodone.

Q. My question is OxyContin.

A. But, the WHO ladder never talks about OxyContin, it only talks about oxycodone. It never uses brand names.

Q. I accept that. I am just asking you a question. If you know whether or not OxyContin, the drug OxyContin --

A. It wouldn't, we don't include it in the list because it is not a generic drug.

Oxycodone, we don't use any of those. We don't use any label to a name and that's the name of a drug. So I am going with oxycodone because that's where the data is.

Q. Do you know whether OxyContin is indicated for mild pain?

A. I think that it is not. I think it's indicated for moderate to severe pain.

Q. In your clinical practice, do you know how many patients had been prescribed OxyContin versus other opioids?

A. In our clinical setting?

Q. In your clinical setting.

A. On an outpatient setting, oxycodone has been a commonly used drug and then those patients take OxyContin. I would have to look to tell you the number. I don't think I know that offhand.

Q. And, certainly in 1985 -- you started practicing medicine at Sloan-Kettering in what, 19 --

A. I was at Memorial appointed in 1974.

Q. And, so you had been practicing medicine in cancer pain for some years before 1985; is that correct?

A. From 1974 to 1985.

Q. And, you had a significant experience with treating patients with cancer pain as of 1985; isn't that correct?

A. And non-malignant pain.

Q. And that was at the time you wrote the articles we talked about earlier today; is that correct?

A. That is correct.

MR. COLANTONIO: Those are all the questions I have.

MR. HOFFMANN: I just have one question and I am not going to move, if you could look at the camera when you respond.

RECROSS EXAMINATION

BY MR. HOFFMANN:

Q. Your expert disclosure that Mr. Colantonio talked about contains this sentence. Tolerance varies enormously among patients, do you agree with that?

A. Yes, I do.

Q. And, to the extent that there is individual patient variation, is tolerance predictable or unpredictable on a patient by patient basis?

A. In the individual patient, the

development of tolerance is very unpredictable.

Q. But, if opioids are taken at a sufficiently high dose in general, is it predictable that some degree of tolerance will occur?

A. Yes.

MR. HOFFMANN: That's all I have.

REDIRECT EXAMINATION

BY MR. COLANTONIO:

Q. Sufficiently high dose being more than what, the 30 milligrams you talked about earlier, a day?

A. Yes.

MR. COLANTONIO: Thank you. That's all the questions I have.

THE VIDEOGRAPHER: Going off the record, 12:05 p.m.

MR. HOFFMANN: Unless anyone on the phone wants to chime in.

(Whereupon, Ms. Lyons ordered a dirty disc, regular copy and minuscript expedited. Mr. Hoffmann ordered a dirty disc only. Mr. Colantonio ordered the transcript regular delivery with a minuscript and Mr. Farrell ordered a minuscript and ASKII.)

C E R T I F I C A T E

I, Susan Wandzilak, Registered Professional Reporter and Notary Public in and for the State of Connecticut do hereby certify that the foregoing pages are a true and accurate transcription of my stenographic notes taken of these proceedings.

I further certify that I am not related nor in any way interested in the outcome of this case.

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SUSAN WANDZILAK